ACTOS® FAMILY CLINICAL UPDATE: MONTANA STATE MEDICAID

MARCH 2008

The ACTOS family of products provides 3 options for the treatment of type 2 diabetes mellitus (T2DM): ACTOS (pioglitazone hydrochloride), ACTO*plus* met™ (pioglitazone hydrochloride and metformin hydrochloride), and DUETACT™ (pioglitazone hydrochloride and glimepiride). Information regarding the indication and mechanism of action for each product is provided in the table below.

Indication and Mechanism of Action for ACTOS Family Products.(1, 2,3)

Product	Indication	Mechanism of Action
ACTOS	Once daily monotherapy and in combination with a sulfonylurea, metformin, or insulin when diet and exercise plus the single agent do not result in adequate glycemic control.	Decreases insulin resistance in the periphery and in the liver resulting in increased insulin-dependent glucose disposal and decreased hepatic glucose output.
ACTO*plus* met	An adjunct to diet and exercise to improve glycemic control in patients with T2DM who are already treated with a combination of ACTOS and metformin or whose diabetes is not adequately controlled with metformin alone, or for those patients who have initially responded to ACTOS alone and require additional glycemic control.	Thiazolidinediones (ACTOS)--see above. Biguanides (metformin) act primarily by decreasing endogenous hepatic glucose production.
DUETACT	An adjunct to diet and exercise as a once-daily combination therapy to improve glycemic control in patients with T2DM who are already treated with a combination of ACTOS and SU or whose diabetes is not adequately controlled with a SU alone, or for those patients who have initially responded to ACTOS alone and require additional glycemic control.	Thiazolidinediones (ACTOS)--see above. Sulfonylureas (glimepiride), an insulin secretagogue, act primarily by stimulating insulin release from functioning pancreatic beta cells.

SU=sulfonylurea.

Clinical Update

The following summarizes the clinical information released since the previous 2007 submission of the ACTOS clinical update. Formulary dossiers containing complete product information for ACTOS, ACTO*plus* met, and DUETACT are available upon request. Please refer to the enclosed package inserts for complete safety information.

Prospective Cardiovascular Outcomes Study

In the **PRO**spective pioglit**A**zone **C**linical **T**rial In macro**V**ascular **E**vents study (PROactive), 5238 patients with T2DM and a prior history of macrovascular disease were treated with ACTOS (n=2605), force-titrated up to 45 mg once daily, or placebo (n=2633).(1)

- A prespecified subgroup analysis of PROactive patients with previous myocardial infarction (MI) (≥6 months before study entry) demonstrated a significant risk reduction of 28% (HR 0.72; *P*=0.045) for time to fatal/nonfatal MI with ACTOS compared to placebo.(4) Acute coronary syndrome (ACS) also had a significant risk reduction of 37% (HR 0.63; *P*=0.035).
- In the PROactive heart failure subanalysis, more patients receiving ACTOS than placebo experienced non-serious heart failure (6.4% vs. 4.3%; p=0.001) as well as serious heart failure (5.7% vs. 4.1%, respectively; *P*=0.007).(5) However, mortality was similar between the groups (0.96% for ACTOS vs. 0.84% for placebo; *P*=0.639).

Observational Studies and Meta-analyses

- A meta-analysis of the ACTOS clinical trial database found that ACTOS was associated with a lower risk of death, MI, and stroke (hazard ratio [HR] 0.82; 95% confidence interval [CI] 0.72-0.94; *P*=0.005). In this study, the occurrence of serious heart failure was increased by ACTOS (HR 1.41; 95% CI 1.14-1.76; *P*=0.002), however, an associated increase in mortality was not observed.(6)

- A meta-analysis of thiazolidinedione (TZD) studies found an increased risk of congestive heart failure with TZD treatment compared with a control group (relative risk [RR] 1.72; 95% CI 1.21-2.42; *P*=0.002). However, the risk of cardiovascular death was not increased by TZD use compared with control (RR 0.93; 95%CI 0.67-1.29; *P*=0.68).(7)
- A retrospective cohort study reported that ACTOS was associated with a 22% risk reduction of hospitalization for acute myocardial infarction (AMI) and a 15% lower rate in the composite endpoint of AMI or coronary revascularization.(8)
- Another nested, case-control study observing elderly patients with diabetes taking TZDs, (mainly rosiglitazone), reported an increased risk of CHF, AMI, and mortality compared with other combination oral antidiabetic treatments.(9)

Prescribing Information Updates for 2007

WARNING: Congestive Heart Failure

- Thiazolidinediones, including ACTOS, cause or exacerbate congestive heart failure in some patients.(1) After initiation of ACTOS, and after dose increases, observe patients carefully for signs and symptoms of heart failure (including excessive, rapid weight gain, dyspnea, and/or edema). If these signs and symptoms develop, the heart failure should be managed according to the current standards of care. Furthermore, discontinuation or dose reduction of ACTOS must be considered.
- ACTOS is not recommended in patients with symptomatic heart failure.(1) Initiation of ACTOS in patients with established NYHA Class III or IV heart failure is contraindicated.

Fracture

In the prospective cardiovascular outcomes study, PROactive, an increased incidence of bone fracture was noted in female patients taking ACTOS.(1) During a mean follow-up of 34.5 months, the incidence of bone fracture in females was 5.1% (44/870) for ACTOS versus 2.5% (23/905) for placebo. This difference was noted after the first year of treatment and remained during the course of the study. The majority of fractures observed in female patients were nonvertebral fractures including lower limb and distal upper limb. No increase in fracture rates was observed in men treated with ACTOS 1.7% (30/1735) versus placebo 2.1% (37/1728). The risk of fracture should be considered in the care of patients, especially female patients, treated with ACTOS and attention should be given to assessing and maintaining bone health according to current standards of care.

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1 ACTOS Prescribing information. Deerfield, IL: Takeda Pharmaceuticals America, Inc.; 2007.
2 ACTOplus met [package insert]. Deerfield, IL: Takeda Pharmaceuticals America, Inc.; 2007.
3 DUETACT [package insert]. Deerfield, IL: Takeda Pharmaceuticals America, Inc.; 2007.
4 Erdmann E, Dormandy JA, Charbonnel B, et al on behalf of the PROactive investigators. The effect of pioglitazone on recurrent myocardial infarction in 2445 patients with type 2 diabetes and previous myocardial infarction: results from the PROactive (PROactive 05) study. *J Am Coll Cardiol*. 2007;49:1772-1780.
5 Erdmann E, Charbonnel B, Wilcox RG, et al. Pioglitazone use and heart failure in patients with type 2 diabetes and preexisting cardiovascular disease: data from the PROactive study (PROactive 08). *Diabetes Care.* 2007;49:1772-1780.
6 Lincoff MA, Wolski K, Nicholls SJ, Nissen SE. Pioglitazone and risk of cardiovascular events in patients with type 2 diabetes mellitus. *JAMA*. 2007;298:1180-1188.
7 Lago RM, Singh PP, Nesto RW. Congestive heart failure and cardiovascular death in patients with prediabetes and type 2 diabetes given thiazolidinediones: a meta-analysis of randomized clinical trials. *Lancet*. 2007;370:1129-1136.
8 Gerrits CM, Bhattacharya M, Manthena S, Baran R, Perez A, Kupfer S. A comparison of pioglitazone and rosiglitazone for hospitalization for myocardial infarction in type 2 diabetes. *Pharmacoepidemiol and Drug Saf*. 2007;16:1065-1071.
9 Lipscombe LL, Gomes T, Lévesque LE, Hux JE, Jurrlink DN, Alter DA. Thiazolidinediones and cardiovascular outcomes in older patients with diabetes. *JAMA*. 2007;298:2634-2643.